

# A two-part mixed-effects model for semi-continuous data to describe the effect of transdermal rotigotine on restless legs symptoms in adults

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## Objectives

To quantify the dose-exposure-response relationship of rotigotine in adult patients suffering from restless legs syndrome (RLS) and to assess the expected efficacy response to daily administration of rotigotine transdermal patches at different dose levels via simulations.

## Methods

### DATA

Pharmacokinetic (PK) and efficacy data from 3 large placebo-controlled clinical trials in adult RLS patients were used. Rotigotine dose was up-titrated during the first 2 to 4 weeks until the target maintenance dose was reached. Patients continued treatment on the maintenance dose level for 6 months in the two phase 3 studies, and for 1 month in the phase 2 dose-ranging study. At the end of the study the dose was reduced in a step-wise fashion during the taper period. PK samples were taken from about 20% of the patients in the phase 3 studies and from all patients in SP709.

Study reference	SP790	SP792	SP709
Number of patients (randomized)	458	505	341
Dose levels (mg/24h)	Placebo, 1, 2, 3	Placebo, 0.5, 1, 2, 3	Placebo, 0.5, 1, 2, 3, 4
Treatment duration (titration/maintenance/taper period)	3 weeks/ 6 months/ 7 days	4 weeks/ 6 months/ 7 days	2 weeks/ 1 month/ 7 days
Number of patients with PK data (excl. placebo)	72	91	276
Number of PK samples per patient	3	3	2
Number of IRLS assessments per patient	11	12	7

The dataset used for modeling included all patients receiving placebo and all patients receiving active treatment who had at least one valid PK measurement (N=709). Data from the remaining patients (N=582) were retained for external validation of the model.

### PK MODEL

A simple PK model was developed to describe the average concentration at steady state ( $C_{av,ss}$ ). Given the transdermal application of rotigotine the fluctuation of plasma concentrations within a dosing interval was low, such that the measured trough levels are a reasonable representation of average concentrations.

$$C_{av,ss} = \frac{DOSE}{CL/F \times 24h}$$

### PKPD MODEL

A two-part mixed-effects model for semi-continuous data [1] was employed, linking predicted  $C_{av,ss}$  to International Restless Legs Syndrome Rating Scale (IRLS) score. The IRLS has been used in clinical trials with dopamine agonists (e.g. cabergoline, pergolide, ropinirole, and pramipexole) and represents an increasingly accepted international standard for the clinical assessment of RLS severity [2]. IRLS scores were transformed to the logit-scale to avoid predictions outside of the range of the scale (0 [no symptoms] – 40 [most severe]).

IRLS scores >0 were treated as continuous data with sub-models for the placebo effect ( $PL_{effect}$ ) and the concentration-response relationship ( $Drug_{effect}$ ):

$$\text{logit}(IRLS) = \text{logit}(\text{Baseline}) + PL_{effect} + Drug_{effect}$$

where  $PL_{effect}$  was described with an exponential function estimating a maximum placebo effect (Pmax) and a half-life to develop Pmax (PHL):

$$PL_{effect} = \text{logit}(Pmax) \times \left(1 - \exp\left(-\frac{\ln(2)}{PHL} \times \text{time}\right)\right)$$

An Emax function was used to model the concentration effect relationship of rotigotine:

$$Drug_{effect} = \text{logit}(Emax) \times \frac{C_{av,ss}}{EC50 + C_{av,ss}}$$

where EC50 is the concentration at 50% of the maximal drug effect.

For IRLS scores equal to zero the probability of such observations ( $Pr_0$ ) was modeled with a logistic regression function incorporating a time and concentration effect:

$$Pr_0 = \frac{\exp(\text{logit}(Pr0max'))}{1 + \exp(\text{logit}(Pr0max'))} \times \left(1 - \exp\left(-\frac{\ln(2)}{PrHL} \times \text{time}\right)\right)$$

where the maximal probability of IRLS scores of 0 is a function of  $C_{av,ss}$ :

$$\text{logit}(Pr0max') = \text{logit}(Pr0max) + PrSlope \times C_{av,ss}$$

The F\_FLAG functionality in NONMEM 7.2 was used for the simultaneous modeling of categorical and continuous data where an indicator variable (TYPE) in the dataset informs NONMEM for which records to apply the continuous or categorical model.

Inter-individual variability was only estimated on the parameters of the continuous model part, not on the logistic regression part.

Residual unexplained variability was modelled as an additive error on the logit-scale.

### SIMULATIONS

The response at different dose levels was simulated using Simulo 6.2 [3]. Simulo is a new tool for complex clinical trial simulations with a graphical user interface to facilitate scenario set-up and R as the calculation backend. One hundred patients were simulated per dose level in each of the 500 trial replicates. Uncertainty in the parameter estimates as well as variability was taken into account in the simulations. Dropout of patients was also accounted for with a Weibull time-to-event dropout model (not shown) where the likelihood of discontinuation increases with increasing IRLS scores.

## Results

### PK MODEL

An allometric relationship between body weight and apparent clearance with a fixed exponent of 0.75 significantly improved the fit of the PK model. A significant study-effect was also identified, showing a 37% lower CL/F in patients from study SP790. The reason for this is unclear, however.

### PKPD MODEL

The disproportionately large number of IRLS scores of 0 in the dataset that required a separate handling of these observations from scores >0 is illustrated in Figure 1. Figure 2 shows how the frequency of the 0-observations varied with time and dose. The maximum probability of IRLS scores of 0 ( $Pr0max$ ) was estimated at 13.5% in absence of drug; the half-life to reach the maximum was, coincidentally, 13.5 days. In Figure 3 the change in  $Pr0max$  as a function of dose (and hence  $C_{av,ss}$ ) is illustrated for a typical patient.

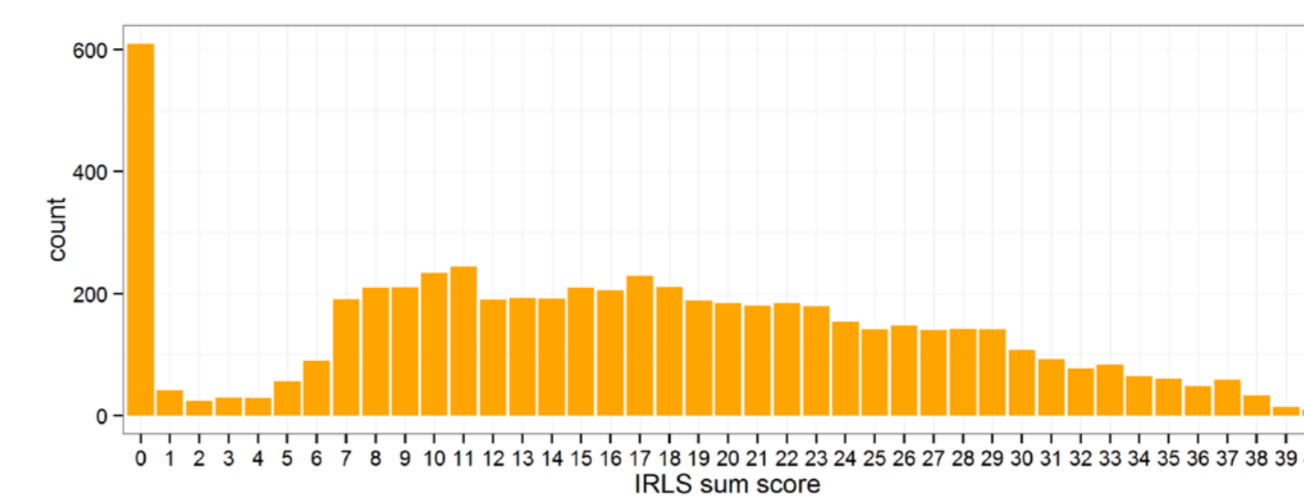


Figure 1 Disproportionally high frequency of IRLS scores of 0 in the dataset.

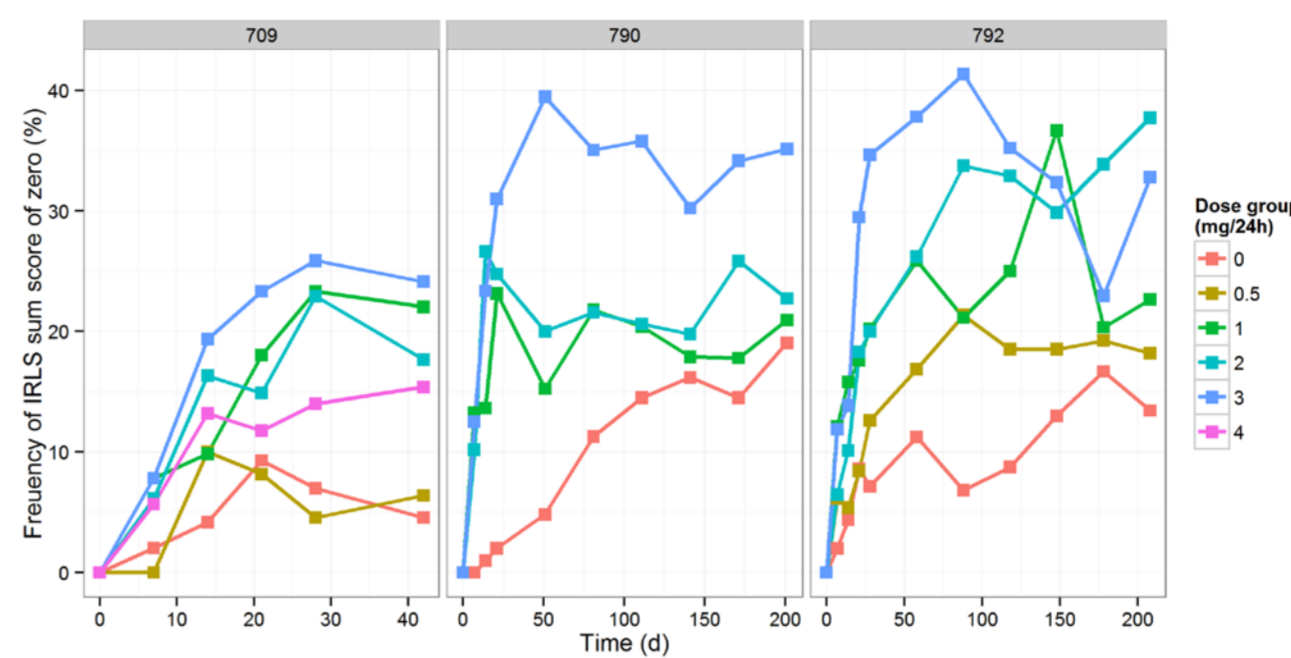


Figure 2 The frequency of IRLS scores of 0 increases with time up to a plateau and is also dependent on the dose.

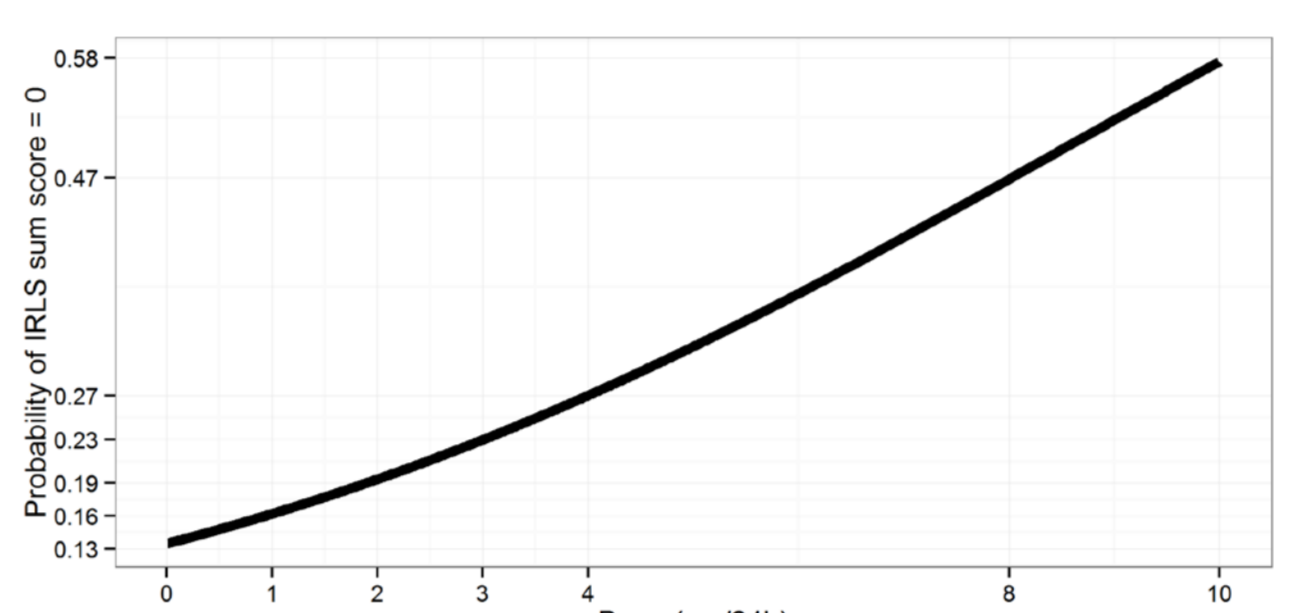


Figure 3 Predicted maximal probability of IRLS sum score of 0 at different doses for a typical patient receiving rotigotine. Note, doses >4 mg/24h were not studied.

IRLS scores >0 were best described with an Emax-type drug effect model and an exponential function for the placebo effect. A lower baseline IRLS score was estimated for patients in SP792 (24.1) compared to the patients from the two other studies (29.5). The effect developed over time with a half-life to reach the maximum of 2.8 days. For the drug effect an EC50 of 0.218 ng/mL was estimated, corresponding to a dose of about 1.5 mg/24h in a typical patient.

The visual predictive check on the validation dataset (i.e. data not used for modeling) demonstrated close correspondence between observed and simulated IRLS scores (Figure 4).

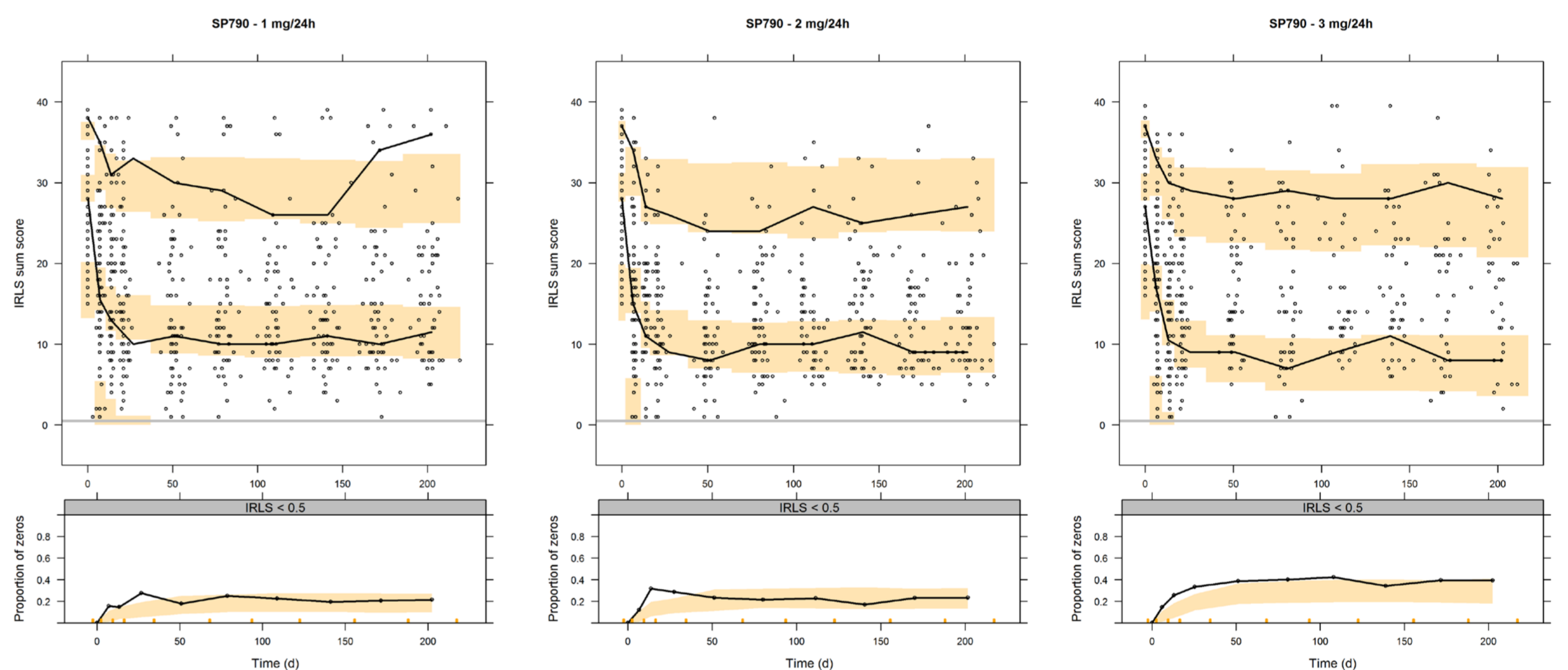


Figure 4 Visual predictive check for SP790 validation data. Top panels show the 5th, 50th and 95th percentiles of the simulated (colored area: 95% CI around the percentiles) and observed (solid line) IRLS sum scores > 0.5. Bottom panels show the proportion of simulated (colored area: 95% CI) and observed (solid line) IRLS sum scores < 0.5. Note, for practical purposes predicted IRLS scores <0.5 were considered 0.

Clinical trial simulations were conducted to illustrate the dose-response curve and to derive the probability for a change of IRLS score over placebo > 3 as a function of dose after 6 months of treatment. Like in the original studies, missing observations due to dropout were imputed applying the 'Last observation carried forward' method.

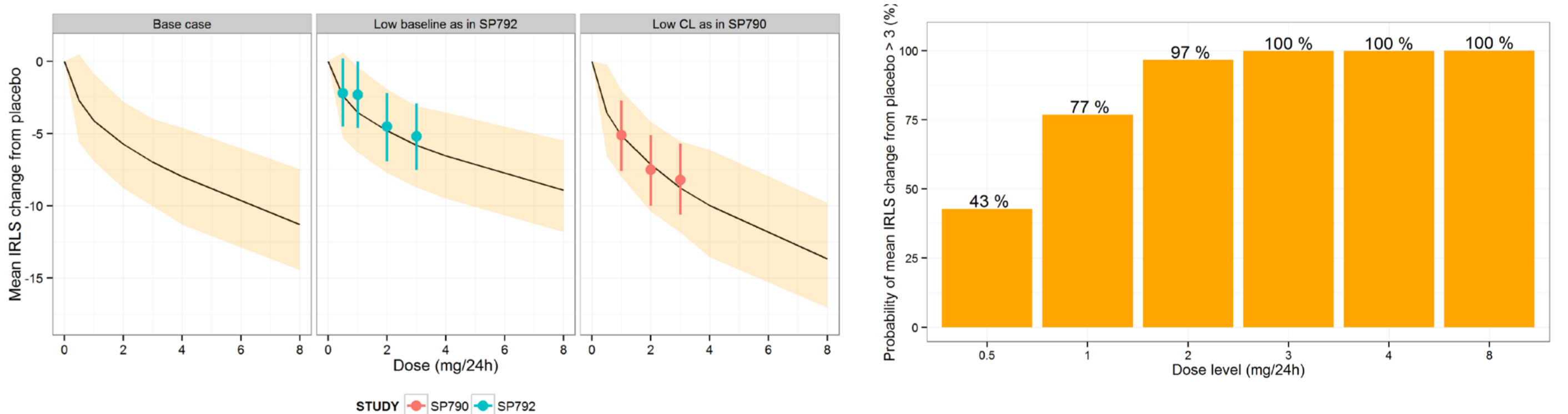


Figure 5 Simulated change in IRLS score from placebo after 6 months as a function of dose. Black solid lines are the mean of the simulations with the 95% confidence band around it (shaded area). The error bars are the 95% CI around the observed mean response of the respective studies.

Figure 6 Probability of mean IRLS change from placebo to exceed a clinically relevant target of 3 (base case scenario).

## Conclusions

- A clear exposure-response relationship between rotigotine  $C_{av,ss}$  and the accepted standard measure of restless legs syndrome severity (IRLS score) could be established.
- The two-part mixed-effect model previously described by Olsen et al.[1] was successfully implemented in NONMEM and proved useful in modeling data with observations at the boundary of the measurement scale.
- The concentration-IRLS model provides a framework to simulate the expected response to rotigotine administration in other populations in order to aid in designing future clinical studies.

## References

- Olsen M, Schafer J. A two-part random-effects model for semicontinuous longitudinal data. J Am Stat Assoc (2001) 96:730–45.
- The International Restless Legs Syndrome Study Group. 2003. Validation of the International Restless Legs Syndrome Study Group rating scale for restless legs. Sleep Med 4:121-132.
- http://www.simulo.eu

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